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10/529,431	03/25/2005	Gregoire Prevost	117P/PCT2/US	6671

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EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 12/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/529,431	PREVOST ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,26,30-34 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,26,30-34 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *April 21, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a national stage application of PCT/IB03/04922, filed September 29, 2003, which claims benefit of provisional application 60/414103, filed September 27, 2002. Claims 1-22, 26, 30-34, and 38 are pending in this application and examined on the merits herein. Applicant's preliminary amendment submitted March 25, 2005 is acknowledged wherein claims 12-14, 20, 22, and 26 are amended, claims 23-25, 27-29, 35-37, and 39-40 are cancelled, and the specification is amended to indicate continuity.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 20, 30-33, and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a pharmaceutical composition comprising a farnesyl transferase inhibitor of formula (I) and an anthracycline, does not reasonably provide enablement for a composition comprising any farnesyl transferase inhibitor or prodrug thereof and an anthracycline or prodrug thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a

disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a pharmaceutical composition comprising two therapeutic agents.

The state of the prior art: Farnesyl transferase is known in the prior art to be involved in the process of tumorgenesis, and certain specific farnesyl transferase inhibitors have demonstrated activity, either alone or in combination with an antitumor agent such as an anthracycline, in halting growth of tumors. Thus the prior art provides a motivation for combining anthracycline and certain farnesyl transferase inhibitors to form an anti-tumor pharmaceutical composition.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The pharmaceutical art is unpredictable in that there exist various factor influencing whether a particular compound exerts the desired therapeutic activity *in vivo*. For example, different compounds localize to different areas of the body, are metabolized at different rates into different metabolites, and have different pharmacokinetic and pharmacodynamic interactions with other active agents.

Furthermore, the art of organic synthesis is unpredictable in that different compounds will require completely different synthetic schemes to obtain them. Novel synthetic schemes are complex and require unpredictable experimentation to put into practice.

The Breadth of the claims: The claimed invention is extremely broad, encompassing farnesyl transferase inhibitors of all sorts, including organic small molecules, polypeptides, polynucleotides, inorganic complexes, siRNA, and anti-farnesyl transferase antibodies, for example. Furthermore, the claimed invention includes compositions comprising as yet unknown farnesyl transferase inhibitors.

The amount of direction or guidance presented: Applicant's specification describes a specific class of farnesyl transferase inhibitors which are useful for inhibiting the growth of nasopharyngeal carcinoma cells. The specification does not disclose any generic teaching as to the full scope of all possible farnesyl transferase inhibitors or their possible application to the treatment of cancer. Further, the specification does not give any teaching which would enable one skilled in the art to ascertain the full scope of all possible farnesyl transferase inhibitors or to synthesize all such compounds.

The presence or absence of working examples: Pp. 47-49 of the instant specification disclose the cytotoxic effect of a combination of doxorubicin and the farnesyl transferase inhibitor known as compound A. No working examples are given for the combination of an anthracycline and ant other farnesyl transferase inhibitor.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the synthesis of a broad range of novel compounds. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of farnesyl transferase inhibitors beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is useful as a farnesyl transferase inhibitor. According to the 2006 Chemical Abstracts catalog, The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to have farnesyl transferase inhibition activity. For most compounds, it is unknown whether they are or are not useful as farnesyl transferase inhibitors. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds for farnesyl transferase inhibitory activity, as well as *in vivo* testing of compounds having this activity involving animal subjects, probably mouse xenografts, to determine therapeutic utility. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and

other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential farnesyl transferase inhibitors, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, dissection, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible farnesyl transferase inhibitors, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of farnesyl transferase inhibitors claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the lack of guidance from Applicant's specification, Applicants fail to provide information sufficient to practice the claimed invention for farnesyl transferase inhibitors other than those of formula (I).

Claims 1-17, 20-22, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising the disclosed active agents and methods comprising administering said compositions, does not reasonably provide enablement for compositions comprising in which one or more

components is a prodrug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a pharmaceutical composition comprising two therapeutic agents.

The state of the prior art: Although some prodrugs are known in the art, prodrugs of the claimed compounds are not known in the art. Methods for designing prodrugs for all such compounds are also not known in the art.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: The art of prodrug design is also highly unpredictable. A prodrug is any compound which is metabolized *in vivo* into a desired active agent. Because there exist so many different metabolic pathways *in vivo*, involving so many different highly specific enzymes, one of ordinary skill in the art would

not be able to accurately predict which compounds would or would not function as prodrugs of a particular compound *in vivo*.

The Breadth of the claims: The claimed invention encompasses any compound acting as a prodrug of the disclosed active agents *in vivo*, regardless of the structure of the compound or the manner it is converted into the active agent.

The amount of direction or guidance presented: Applicant's disclosure gives no guidance as to which compounds are expected to be prodrugs of the disclosed active agents.

The presence or absence of working examples: No working examples of prodrugs are provided.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the design of prodrugs. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of prodrugs encompassed by the instant claims would be required to test potential compounds *in vivo* to determine whether a particular compound is in fact metabolized into one of the desired compounds. For most compounds, it is unknown whether there exist any species from which they may be metabolized *in vivo*. Gathering this data for every compound which could reasonably be expected to be a prodrug would involve *in vitro* screening of an enormous diversity of chemical compounds for their metabolic fate *in vivo*. As described earlier, synthesis of diverse chemical structures requires novel and

unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential prodrugs, these animal experiments would need to be repeated hundreds of times, and involve the maintenance, killing, and disposal of thousands of experimental animals, to establish the activity or lack thereof of every possible farnesyl transferase inhibitors, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of farnesyl transferase inhibitors claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention for prodrugs of farnesyl transferase inhibitors or anthracyclines.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-22, 26, 30-34, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gordon et al. (PCT international publication WO00/39130, included by Applicant with PTO-1449) in view of Rybak. (PCT international publication WO01/64197, included with PTO-1449) Gordon et al. discloses a pharmaceutical composition comprising one of a variety of compounds having an identical formula to formula (I) recited in instant claim 2. (pp. 2-9) Further specifically recited embodiments include the farnesyl transferase inhibitors of instant claims 3-17. (pp. 17-27) These compounds are disclosed to possess anti-tumor activity (p. 16, lines 16-29) and to be useful for inhibiting prenyl transferases including farnesyl transferase. (p. 9, lines 8-25) Gordon et al. does not disclose a pharmaceutical composition comprising a combination of compound according to structure (I) and an anthracycline, or a method of treating nasopharyngeal cancer by administering such a composition to a subject. Gordon et al. also does not disclose a pharmaceutical kit comprising such a composition according to instant claims 34 and 38.

Rybak discloses therapeutic combinations of anthracyclines and farnesyl transferase inhibitors which are effective in the inhibition of tumor cell growth. (p. 13, lines 3-6) Preferred anthracycline derivatives include daunorubicin, doxorubicin, and

idarubicin. (p. 21, lines 24-26) These compositions may be used in a method of inhibiting abnormal cell growth or treating various cancers, (p. 22, lines 12-38) in a mammal, particularly a human. The two components may be administered either simultaneously or sequentially. (p. 23, lines 16-18)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a pharmaceutical composition comprising a farnesyl transferase inhibitor according to Gordon et al. and further comprising an anthracycline such as doxorubicin. It would also have been obvious to administer this combination to a patient suffering from nasopharyngeal carcinoma. It would further have been obvious to prepare the composition in the form of a kit comprising a container and instructions for using he composition. One of ordinary skill in the art would have been motivated to combine the two components and to administer them to a patient suffering from nasopharyngeal carcinoma because both components were known to be useful for the treatment of cancer broadly. One of ordinary skill in the art would have reasonably expected success because both compounds were known to be useful for the same purpose. It has been held that it is *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose in order to practice a third composition for the very same purpose. The idea of combining them flows logically from their having been taught individually in the prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Further, with respect to the kits described in instant claims 34 and 38, a pharmaceutical kit or the patient pack comprising the same combination pharmaceutical

composition in two dosage forms and directions for administering the dosage forms are all deemed obvious since they are all within the knowledge and conventional skills of pharmacologist to conveniently assist the user and prescriber for easy dispensary of the medication. Moreover, the inclusion of a package inserts including "indication and use" of the pharmaceutical composition in a pharmaceutical kit is mandated by 21 CFR 201.57 according to *Remington: The Science and Practice of Pharmacy*. Furthermore, with respect to the instructions or directions that direct one on how to use in a kit, the U.S. Court of Appeals for the Federal Circuit, *In re Ngai* 03-1524, recently rules that a kit of the prior art with a set of instructions is unpatentable (see the precedential opinion issued May 13, 2004).

Thus the invention taken as a whole is *prima facie* obvious.

Summary

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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